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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,381	06/10/2005	Guenther Eissner	021149-000001	4749
24239	7590	05/23/2008	EXAMINER	
MOORE & VAN ALLEN PLLC			BOWMAN, AMY HUDSON	
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Research Triangle Park, NC 27709			ART UNIT	PAPER NUMBER
			1635	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/516,381	EISSNER ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	AMY H. BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 06 March 2008.  
 2a) This action is **FINAL**.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 3-5 and 7-19 is/are pending in the application.  
 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 3-5 and 7-19 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on 30 November 2004 is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) Notice of References Cited (PTO-892)  
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
 3) Information Disclosure Statement(s) (PTO/SB/08)  
 Paper No(s)/Mail Date 1/11/05, 4/28/05.

4) Interview Summary (PTO-413)  
 Paper No(s)/Mail Date. \_\_\_\_\_.  
 5) Notice of Informal Patent Application  
 6) Other: \_\_\_\_\_.

## **DETAILED ACTION**

Applicant's election without traverse of group III, claims 3 and 17 in the reply filed on 10/19/07 is acknowledged. Applicant amended claims 4, 5, 7-9, 11 and 18. As instantly recited, claims 3-5 and 7-19 are directed to the elected invention.

In response to the supplemental restriction requirement mailed on 12/7/07, applicant's election without traverse the species "5-fluorouracil" in the reply filed on 3/6/08 is acknowledged.

The subject matter of the claims that is not directed to the elected invention is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/7/07.

### ***Information Disclosure Statement***

The information disclosure statements (IDS) submitted on 1/11/05 and 4/28/05 have been considered by the examiner.

### ***Specification***

If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 365(c) and 119(e), a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or

365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

If the instant application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional

information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

### ***Claim Objections***

Claims 8-12 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claims 8-12 recite the sequence of administering the immunosuppressant and the protective oligodeoxyribonucleotide. However, the claims depend from claim 3, which is directed to a method of treating a patient "undergoing treatment with an immunosuppressant" comprising administering a protective oligodeoxyribonucleotide.

Since claim 3 requires that the patient is already undergoing treatment with the immunosuppressant, claims 8-12 do not further limit claim 3. Therefore, claims 8-10 recite embodiments of administering the protective oligodeoxyribonucleotide after the immunosuppressant, which is already required by claim 3. Claims 8, 11 and 12 recite embodiments of administering the protective oligodeoxyribonucleotide before the immunosuppressant, which conflicts with the requirement of claim 3 and broadens the scope of the invention.

Importantly, claim 3 does not recite a step of administering the immunosuppressant, but only recites a step of administering the protective oligodeoxyribonucleotide.

Claims 3-5 and 7-19 are objected to because of the following informalities: It appears that applicant inadvertently omitted the word "of" between "protection" and "one" in claim 3. Claims 4, 5 and 7-19 are objected to because they depend from claim 3. Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-5, 8-12 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

At the outset, it is noted that the claims do not recite a specific “protective oligodeoxyribonucleotide”, but rather refer to an extremely broad genus of oligodeoxyribonucleotides.

The claims encompass a method of treating a patient undergoing treatment with an immunosuppressant via administering any protective oligodeoxyribonucleotide and achieving protection of one or both of the patient’s epithelial or endothelial cells from one or both of apoptosis or activation induced by the immunosuppressant.

Although the specification discloses that fludarabine activates and damages endothelial and epithelial cells, leading to damage in situations where fludarabine is utilized for treatment, and that these cells can be protected by treatment with defibrotide, the specification does not describe an adequate species of “protective oligodeoxyribonucleotides” to demonstrate that applicant was in possession of the claimed genus of oligodeoxyribonucleotides within the instant method at the time the invention was made. The instant genus of protective oligodeoxyribonucleotides is very large, including antisense oligonucleotides, siRNAs, aptamers, triplexes, peptides, and miRNAs, for example.

Applicant has not described a structure that would allow the skilled artisan to envision which oligodeoxyribonucleotides are considered protective and would have the desired outcome of achieving protection of one or both of the patient’s epithelial or

endothelial cells from one or both of apoptosis or activation induced by the immunosuppressant, such that the skilled artisan would recognize that applicant was in possession of the claimed scope at the time the invention was filed.

Additionally, the instant specification does not clearly define "protective oligodeoxyribonucleotide". Since the specification does not sufficiently describe the term "protective oligodeoxyribonucleotide", and specifically what the oligodeoxyribonucleotide is protective of, the skilled artisan would not be able to readily envision the scope of "protective oligodeoxyribonucleotide" in order to appreciate that the applicant was in possession of this genus within the instant method.

The instant specification does not define "activation" as recited in instant claim 3 and thus the skilled artisan would not be able to readily envision the scope of "activation" in order to appreciate what is being activated by the administration of the immunosuppressant. This terminology is being interpreted as activation of an immune response.

Claims 3-5 and 7-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of administering defibrotide to a patient undergoing treatment with fludarabine and resultant inhibition of fludarabine induced apoptosis, wherein fludarabine induces ICAM-1 expression, does not reasonably provide enablement for a method of administering any protective oligodeoxyribonucleotide to a patient undergoing treatment with any

immunosuppressant with the resultant desired effects . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

*In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The instant claims are directed to a method of treating a patient undergoing treatment with any immunosuppressant comprising administering any protective oligodeoxyribonucleotide with the outcome of protecting one or both of the patient's epithelial or endothelial cells from one or both of apoptosis or activation induced by the administration of the immunosuppressant.

The instant specification teaches delivering defibrotide in vitro in cultured endothelial cells treated with fludarabine and resultant inhibition of fludarabine induced apoptosis, wherein fludarabine induces ICAM-1 expression. Although the exemplification of the instant specification is strictly in vitro, the art teaches in vivo

treatment of a patient with daunorubicin and etoposide, as well as intravenous delivery of defibrotide, as evidenced by Bairey et al. (American Journal of Hematology, April 2002, 69, pages 281-284). Therefore, there is no reason to believe that delivery of 5-fluorouracil, the elected immunosuppressant, or fludarabine, the preferred immunosuppressant of the instant specification that was tested in vitro, would not successfully treat venoocclusive disease in the method of Bairey et al. Therefore, applicant is enabled for in vivo treatment with the instantly recited immunosuppressants and defibrotide.

However, the specification and the state of the art do not reasonably provide enablement for a method of administering any protective oligodeoxyribonucleotide to a patient undergoing treatment with any immunosuppressant with the instantly recited outcome of protection of one or both of the patient's endothelial or epithelial cells from one or both of apoptosis or activation induced by the administration of the immunosuppressant, wherein in one embodiment the activation is enhanced expression of ICAM-1.

There is no guidance in the specification as filed that teaches how to mediate the instant method in a patient with any immunosuppressant, which encompasses any agent that suppresses the immune system in any way, via administering any protective oligodeoxyribonucleotide, which encompasses any oligodeoxyribonucleotide that protects from anything, with a resultant protection of one or both of endothelial or epithelial cells from one or both of apoptosis or activation induced by the administration

of the immunosuppressant, wherein in one embodiment the activation is enhanced expression of ICAM-1.

For example, Korneluk et al. (US 6,300,492 B1) teaches teach that antisense oligonucleotides targeted to IAP result in enhanced apoptosis in epithelial ovarian cancer cells (see examples 2 and 3; as well as claims 1-3 and 8). Korneluk et al. teach that the inhibitor of IAP can be used in a method of treating a patient by inducing apoptosis alone or in combination with other therapies, such as antibody immunosuppressants. Therefore, Korneluk et al. teach an embodiment of the instant claims that does not result in protection of the epithelial cells from apoptosis, but rather enhances apoptosis.

Given the teachings of the specification as discussed above, one skilled in the art could not predict *a priori* whether introduction of any protective oligodeoxyribonucleotide to a patient undergoing treatment with any immunosuppressant would result in each of the instantly recited outcomes. Therefore, to practice the claimed invention, one of skill in the art would have to *de novo* determine which immunosuppressants and which protective oligodeoxyribonucleotides would together act in a manner to achieve the instantly recited outcomes. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed,

would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation (see MPEP 2164.01(a)).

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3 and 7-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Burcoglu et al. (US 5,624,912).

The instant claims are directed to a method of treating a patient undergoing treatment with an immunosuppressant comprising a step of administering to the patient a therapeutically effective dose of a protective oligodeoxyribonucleotide and achieving protection of one or both of the patient's epithelial or endothelial cells from one or both of apoptosis or activation induced by the administration of the immunosuppressant; wherein the activation includes enhanced expression of I-CAM. The claims further specify that the oligodeoxyribonucleotide is defibrotide and specify dosing ranges.

It is noted that Burcoglu et al. is directed to an enabled embodiment of the instant invention, as Burcoglu et al. is directed to a method of delivering a specific immunosuppressant, defibrotide, and a specific protective oligodeoxyribonucleotide, defibrotide via intravenous delivery.

Burcoglu et al. teach a method of treating HIV comprising administering oligodeoxyribonucleotides to a patient in need thereof (see column 5, claims 1 and 2, and example 3, for example). Burcoglu et al. teach that therapeutic nucleic acids such as defibrotide act to revive normal cell function, and act as an immunosuppressant of inappropriately or disproportionately activated cellular repair events (see columns 9 and 24). Therefore, defibrotide meets the instant limitation of an immunosuppressant, as taught by Burcoglu et al. and meets the instant limitation of a protective oligodeoxyribonucleotide, as instantly claimed.

Burcoglu et al. teach various considerations for dosing parameters and teach that bleeding complications occurred at 300 mg/kg/day or above, the maximum tolerable dose (see column 10). Burcoglu et al. teach that initial administration of the defibrotide is followed by incrementally increasing doses until the maximum efficacious dose is reached. Furthermore, Burcoglu et al. teach that an initial bolus of defibrotide is given intravenously over 15-30 minutes, immediately followed by the daily dose of 40-400 mg/kg by continuous infusion. Burcoglu et al. teach that preferably the initial dose is a bolus of 25-50 mg/kg followed by 24-hour dose which is increased in 50 mg/kg/day increments every 1-3 days (see columns 17 and 18). The dosing of Burcoglu et al. anticipates the instant dosing of “about” 15 mg/kg or “about” 100 mg/kg.

Since Burcoglu et al. teaches repeated administration of the defibrotide, the method of Burcoglu et al. meets the instant limitation of administering the immunosuppressant (defibrotide) and the protective oligodeoxyribonucleotide (defibrotide) before and after each other, as well as together.

Since Burcoglu et al. teaches a method comprising each of the instant method steps, the method would necessarily achieve the recited outcome of protection of one or both of the patient's epithelial or endothelial cells from one or both of apoptosis or activation, wherein the activation includes enhanced expression of I-CAM, induced by the administration of the immunosuppressant, absent evidence to the contrary. As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property. Burcoglu et al. teaches a method comprising the instantly recited method steps and therefore anticipates the instant invention, absent evidence to the contrary.

Claims 3, 7-10, and 13-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Sayer et al. (J Cancer Res Clin Oncol, March 2002, 128, pages 148-152).

The instant claims are directed to a method of treating a patient undergoing treatment with an immunosuppressant comprising a step of administering to the patient a therapeutically effective dose of a protective oligodeoxyribonucleotide and achieving protection of one or both of the patient's epithelial or endothelial cells from one or both of apoptosis or activation induced by the administration of the immunosuppressant; wherein the activation includes enhanced expression of I-CAM. The claims further specify that the oligodeoxyribonucleotide is defibrotide and specify dosing ranges.

It is noted that Sayer et al. is directed to an enabled embodiment of the instant invention, as Sayer et al. is directed to treating a specific disease, hepatic veno-occlusive disease, via delivering a specific immunosuppressant, methylprednisolone, and a specific oligodeoxyribonucleotide, defibrotide, via a specific mode of delivery, infusion.

Sayer et al. teach a method of treating a patient undergoing treatment with an immunosuppressant, more specifically methylprednisolone, the method comprising administering defibrotide (see abstract).

Sayer et al. teach administration of the immunosuppressant and defibrotide after allogeneic stem cell transplantation (see abstract). Sayer et al. teach that defibrotide was administered at a dose of 10 mg/kg up to 30/mg/kg per day (see page 149, column 2), which is within the range of the instantly recited dosages. Sayer et al. teach that defibrotide enhances tPA and thrombomodulin in endothelial cell cultures.

Since Sayer et al. teaches a method comprising each of the instant method steps, the method would necessarily achieve the recited outcome of protection of one or both of the patient's epithelial or endothelial cells from one or both of apoptosis or activation, wherein the activation includes enhanced expression of I-CAM, induced by the administration of the immunosuppressant, absent evidence to the contrary. As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property. Sayer et al. teaches a method comprising the instantly recited method steps and therefore anticipates the instant invention, absent evidence to the contrary.

Claims 3-5 and 7-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Bairey et al. (American Journal of Hematology, April 2002, 69, pages 281-284).

The instant claims are directed to a method of treating a patient undergoing treatment with an immunosuppressant comprising a step of administering to the patient

a therapeutically effective dose of a protective oligodeoxyribonucleotide and achieving protection of one or both of the patient's epithelial or endothelial cells from one or both of apoptosis or activation induced by the administration of the immunosuppressant; wherein the activation includes enhanced expression of I-CAM. The claims further specify that the oligodeoxyribonucleotide is defibrotide; the immunosuppressant is a nucleoside and specify dosing ranges.

It is noted that Bairey et al. is directed to an enabled embodiment of the instant invention, as Bairey et al. is directed to treating a specific disease, veno-occlusive disease, via delivering specific immunosuppressants, etoposide or daunorubicin, and a specific oligodeoxyribonucleotide, defibrotide, via a specific mode of delivery, intravenous delivery.

Bairey et al. teach a method of treating a patient undergoing treatment with an immunosuppressant, more specifically etoposide, the method comprising administering defibrotide (see page 282, column 1). Bairey et al. teach administering daunorubicin, another immunosuppressant, after the treatment with defibrotide (see page 282, column 2).

Bairey et al. teach that defibrotide was administered at a dose of 12 mg/kg which was increased gradually to 30 mg/kg (see page 282, column 1), which is within the range of the instantly recited dosages.

Bairey et al. teach that administration of intravenous defibrotide for 19 days induced complete resolution of hepatic venoocclusive disease.

Since Bairey et al. teach a method comprising each of the instant method steps, the method would necessarily achieve the recited outcome of protection of one or both of the patient's epithelial or endothelial cells from one or both of apoptosis or activation, wherein the activation includes enhanced expression of I-CAM, induced by the administration of the immunosuppressant, absent evidence to the contrary. As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property. Bairey et al. teaches a method comprising the instantly recited method steps and therefore anticipates the instant invention, absent evidence to the contrary.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3, 7-16, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sayer et al. (J Cancer Res Clin Oncol, March 2002, 128, pages 148-152).

The instant claims are directed to a method of treating a patient undergoing treatment with an immunosuppressant comprising a step of administering to the patient a therapeutically effective dose of a protective oligodeoxyribonucleotide and achieving protection of one or both of the patient's epithelial or endothelial cells from one or both of apoptosis or activation induced by the administration of the immunosuppressant. The claims further specify that the oligodeoxyribonucleotide is defibrotide and specify dosing ranges.

It is noted that Sayer et al. is directed to an enabled embodiment of the instant invention, as Sayer et al. is directed to treating a specific disease, hepatic veno-occlusive disease, via delivering a specific immunosuppressant, methylprednisolone, and a specific oligodeoxyribonucleotide, defibrotide, via a specific mode of delivery, infusion.

Sayer et al. teach a method of treating a patient undergoing treatment with an immunosuppressant, more specifically methylprednisolone, the method comprising administering defibrotide (see abstract).

Sayer et al. teach administration of the immunosuppressant and defibrotide after allogeneic stem cell transplantation (see abstract). Sayer et al. teach that defibrotide was administered at a dose of 10 mg/kg up to 30/mg/kg per day (see page 149, column 2), which is within the range of the instantly recited dosages. Sayer et al. teach that defibrotide enhances tPA and thrombomodulin in endothelial cell cultures.

Since Sayer et al. teaches a method comprising each of the instant method steps, the method would necessarily achieve the recited outcome of protection of one or both of the patient's epithelial or endothelial cells from one or both of apoptosis or activation induced by the administration of the immunosuppressant, absent evidence to the contrary. As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property.

Sayer et al. do not teach administering the protective oligodeoxyribonucleotide before administration of the immunosuppressant; do not teach treatment with the immunosuppressant during allogeneic stem cell transplantation.

It would have been obvious to administer the protective oligodeoxyribonucleotide before administration of the immunosuppressant in the method of Sayer et al. It would have been obvious to treat the patient of Sayer et al. with the immunosuppressant during allogeneic stem cell transplantation.

With regards to the sequence of administering the protective oligodeoxyribonucleotide before administration of the immunosuppressant in the method of Sayer et al., the specific dosing requirements, and to treat the patient of Sayer et al. with the immunosuppressant during allogeneic stem cell transplantation, it would have been *prima facie* obvious to perform routine optimization of the method, as noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular sequence of administration of the compounds or the dosing requirements used was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Furthermore, Sayer et al. teach administration of the immunosuppressant and defibrotide after allogeneic stem cell transplantation and therefore it would have been obvious to optimize the method via administering the compounds during the allogeneic stem cell transplantation as well.

One would have been motivated to administer the compounds in varying order with varying doses during allogeneic stem cell transplantation, as these are each design choice elements of the method of Sayer et al. One would have been motivated to alter the timing of administration in order to routinely optimize the method of Sayer et al.

There would have been a reasonable expectation of success given each of the elements are basic alterations to the timing of the method of Sayer et al. that are within the realm of routine optimization. The method of Sayer et al. is taught to be successful, so altering the timing and dosing within the method is within the realm of routine optimization.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 3-5 and 7-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bairey et al. (American Journal of Hematology, April 2002, 69, pages 281-284), in view of De Luca et al. (Int. J. Cancer, 1997, 73, pages 277-282).

The instant claims are directed to a method of treating a patient undergoing treatment with an immunosuppressant comprising a step of administering to the patient a therapeutically effective dose of a protective oligodeoxyribonucleotide and achieving protection of one or both of the patient's epithelial or endothelial cells from one or both of apoptosis or activation induced by the administration of the immunosuppressant; wherein the activation includes enhanced expression of I-CAM. The claims further specify that the oligodeoxyribonucleotide is defibrotide; the immunosuppressant is a nucleoside, more specifically 5-fluorouracil and specify dosing ranges.

It is noted that Bairey et al. is directed to an enabled embodiment of the instant invention, as Bairey et al. is directed to treating a specific disease, veno-occlusive

disease, via delivering specific immunosuppressants, etoposide or daunorubicin, and a specific oligodeoxyribonucleotide, defibrotide, via a specific mode of delivery, intravenous delivery.

Furthermore, it is noted that claims 3-5 and 7-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Bairey et al., as explained above. Claim 5 was rejected because Bairey et al. teach administering immunosuppressants that are recited in claim 5. The instant rejection under 35 U.S.C. 103(a) is specific to the elected species of immunosuppressant, 5-fluorouracil, which is not taught by Bairey et al.

Bairey et al. teach a method of treating a patient undergoing treatment with an immunosuppressant, more specifically etoposide, the method comprising administering defibrotide (see page 282, column 1). Bairey et al. teach administering daunorubicin, another immunosuppressant, after the treatment with defibrotide (see page 282, column 2).

Bairey et al. teach that defibrotide was administered at a dose of 12 mg/kg which was increased gradually to 30 mg/kg (see page 282, column 1), which is within the range of the instantly recited dosages.

Bairey et al. teach that administration of intravenous defibrotide for 19 days induced complete resolution of hepatic venoocclusive disease.

Since Bairey et al. teach a method comprising each of the instant method steps, the method would necessarily achieve the recited outcome of protection of one or both of the patient's epithelial or endothelial cells from one or both of apoptosis or activation, wherein the activation includes enhanced expression of I-CAM, induced by the

administration of the immunosuppressant, absent evidence to the contrary. As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property. Bairey et al. teaches a method comprising the instantly recited method steps and therefore anticipates the instant invention.

Bairey et al. does not teach a patient undergoing treatment with 5-fluorouracil.

De Luca et al. teach that 5-fluorouracil is a conventional chemotherapeutic drug (see abstract).

It would have been obvious to practice the method of Bairey et al. of administering defibrotide, wherein the patient is undergoing treatment with 5-fluorouracil.

It would have been *prima facie* obvious to perform routine optimization of the method of Bairey et al. with different known chemotherapeutic drugs, as noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular sequence of administration of the compounds or the dosing requirements used was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

One would have been motivated to practice the method of Bairey et al. wherein the chemotherapeutic drug is 5-fluorouracil because 5-fluorouracil is a known

chemotherapeutic drug to achieve the same desired benefit of treating the leukemia of Bairey et al. Importantly, Bairey et al. teach a method with each of the instantly recited method steps and teach administering defibrotide and chemotherapeutic agents.

Although the chemotherapeutic agents utilized in the method of Bairey et al. are etoposide and daunorubicin, one of skill in the art would certainly be motivated to try other known chemotherapeutic agents as well as a design choice and to optimize the treatment of the method of Bairey et al.

There would have been a reasonable expectation of success given that each of the agents was known to be utilized for the same purpose as chemotherapeutic agents.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY H. BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Amy H. Bowman/  
Examiner, Art Unit 1635